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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/488,737	01/20/2000	Ling Lissolo	50019/008001	4843

7590 08/23/2002

Paul T Clark
Clark and Elbing LLP
176 Federal Street
Boston, MA 02110

EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/23/2002 15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/488,737	Applicant(s) Lissolo et al
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 2, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-7, 10, 11, and 14-32* is/are pending in the application.

4a) Of the above, claim(s) *21, 25-27, 31, and 32* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-7, 10, 11, 14-20, 22-24, and 28-30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1, 3-7, 10, 11, and 14-32* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

New claims 17-32 have been added.

Claims 2,8,9,12-13 have been canceled.

Claims 1,3-7,10-11, 14-32 are pending.

Claims 1,3-7,10-11 and 14-16 have been amended.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections Withdrawn

2. Claim 16 objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim must depend upon other claims in the alternative and it depends upon both claim 1 and claim 10, in light of the amendment of claim 16 to depend only from claim 1.

3. The disclosure objected to because of the following informalities: At page 7, line 5, an amino acid sequence that falls within the sequence rule requirement is recited; it appears to be SEQ ID NO 1, in light of the amendment of page 7, lines 3-19 and the insertion of a SEQ ID NO, and insertion of a header for the Brief Description of the Several Views of the Drawing(s).

4. Claims 7, 9, 11, 13 and 15 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the disclosed proteins of Helicobacter pylori and immunogenic fragments therefrom, does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate

in **scope** with these claims, in light of the cancellation of claims 9 and 13, and the amendment of claim 7, 11 and 15 to be no longer directed to mutant polypeptides and antibodies immunoreactive thereto and the diagnostic method no longer utilizes mutant fragments of a polypeptide in the determining the presence of Helicobacter antibodies.

5. Claims 7-11, 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the cancellation of claims 8-9 and 12-13, and amendment of claims 7, 10-11.

6. Claims 1,2,7-9,15 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrero et al (1995), in light of the cancellation of the species of protein directed to 54 kDa.

7. Claims 1,2, 10 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Leying et al (1992), in light of the cancellation of the species of protein directed to 54 kDa.

8. Claims 1,3-4, 6 rejected under 35 U.S.C. 102(b) as being anticipated by Landini et al (1989), in light of the claim having been amended to recite the presence of a pharmaceutical carrier.

9. Claims 1 and 5 rejected under 35 U.S.C. 102(b), as previously applied to claims 1, 5, 10-15, as being anticipated by Bolin et al (1995), in light of the claim having been amended to recite the presence of a pharmaceutical carrier.

10. Claims 10-11 rejected under 35 U.S.C. 102(b) as being anticipated by Cordle et al (US Pat. 5,260,057), in light of the claims having been amended to recite "consisting essentially of"

Rejections Maintained

11. Claims 14-15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record in paper number 8, paragraph 10.

12. Claims 1,3-7, and newly submitted claims 19, 22-24,28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by **Husson et al** (1993), as previously applied to claims 1-3,5-6 and 8, for reasons of record in paper number 8, paragraph 13.

13. Claims 1, 3-7, 10-11 and 14-19, 22-24, 28-30 rejected under 35 U.S.C. 102(e) as being anticipated by **Calenoff** (US Pat.5,567,594, filing date: December 20, 1993), as previously applied to claims 1-9 and 15, for reasons of record in paper number 8, paragraph 14.

14. New amended or Newly submitted claims 1, 19-20 and 29-30 are rejected under 35 USC 102(b) as being anticipated by **Ferrero et al** (1995), as previously applied to claims 1,2,7-9 and 15, for reasons of record in paper number 8, paragraph 15.

15. Claims 10-11, 14-15 rejected under 35 U.S.C. 102(b), as previously applied to claims 1, 5, 10-15, as being anticipated by **Bolin et al** (1995), for reasons of record in paper number 8, paragraph 17.

16. Claims 1,3-5, 7,10-11 and 14-15 rejected under 35 U.S.C. 102(b) as being anticipated by **Doig et al** (1994), for reasons of record in paper number 8, paragraph 18.

17. Claims 1,5-6, 10-11,and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by **Alemohammad** (US Pat.5,262,156), for reasons of record in paper number 8, paragraph 19.

18. Claims 1, 3-6,7, 19, 20, 22-24, 28-29 are rejected under 35 U.S.C. 102(e) as being anticipated by **Pronovost et al** (US Pat. 5,814,455 and 5,846,751), for reasons of record in paper number 8, paragraph 20.

19. Claims 7, 10, 11, 14, 18, 19, 20,23-24 are rejected under 35 U.S.C. 102(b) as being anticipated by **Ruiz et al** (WO94/06474), for reasons of record in paper number 8, paragraph 22.

Election/Restriction

20. Newly submitted claims 21, 25-27, 31 and 32 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 25-27 and 31-32 are directed to a method not previously examined, and claim 21 recites specific species of antigen and combinations of antigens that have not previously been examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21,25-27, 31-32 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Arguments

21. Applicant's arguments filed January 2, 2002 have been fully considered but they are not persuasive.

22. The rejection of claims 14-15 under 35 U.S.C. 112, second paragraph which recite methods steps in the passive voice, is asserted to have been obviated by amendment of the claims to recite "steps in a positive manner."

23. Upon consideration of the amendments of claims 14 and 15, the examiner found the that the step recited in each method had not been amended to recite an active voice methods step, but still recites the phrases "according to which the biological sample is brought into contact" and "the unbound material is removed".

This rejection could be obviated by amending the claims to recite method steps of --contacting-- and --removing--.

24. At page 13 of Applicant's Reply to Office Action, dated October 21, 2001, all of the prior art rejections are traversed as group and asserts that the instantly claimed invention has been distinguished over the applied prior art through amendment of the claims to recite the phrase "consist essentially of".

25. It is the position of the examiner that composition claims which recite the phrase "consisting essentially of" may have additional components added to the composition as long as the basic and novel characteristic of the composition is maintained. What the basic and novel characteristic of the instantly claimed invention is (protein or polypeptide of Helicobacter pylori)

has not been clearly pointed out and what can and cannot be added to the composition and still maintain the basic and novel characteristic has not been defined.

The phrase "consisting essentially of" is being read as open language as what characteristic of the composition must not be altered has not been defined. What the phrase "consisting essentially of" means with respect to a composition: Ex parte Davis et al., 80 USPQ 448 (Bd); In re JANAKIRAMA-RAO, 137 USPQ 893 (CCPA 1963) is not clear since there is no understanding as to what it means in claims reciting amino acid or nucleic acid sequence, such claims are indefinite (Seq ID No 1 recited in claim 4 which depends from claims 1,3 and 4).

At page 3 of the instant specification, lines 6-10, the definition of the phrase "substantially purified form" is set forth to be mean "the protein is separated from the medium in which it exists naturally. It is the position of the examiner that this definition reads on a whole cell lysate, and the claimed invention is directed to a membrane fraction of this composition, which would define a composition that would contain a plurality of Helicobacter pylori membrane proteins.

In conclusion, it is the position of the examiner that the instantly claimed invention reads on fractioned H.pylori membrane proteins, and antibodies directed to the proteins and fragments of the proteins.

Prior Art Rejections Traversed

26. Applicant traverses all of the applied prior art as not presenting the H.pylori membrane proteins in "pharmaceutically acceptable form".

27. It is the position of the examiner that:

a. (Instant claims 1,3-7, and new claims 19, 22-24,28-29) **Husson et al** (1993) disclose a composition of substantially purified Helicobacter pylori membrane fraction antigens in sterile distilled water (see page 2695, col. 2, paragraph 1, line 11). The membrane fraction protein composition contained proteins of 54, 52, 48, 33, 30 and 29 kDa.

b.(Instant claims 1, 3-7, 10-11 and 14-19, 22-24, 28-30) **Calenoff** (US Pat.5,567,594, filing date: December 20, 1993) disclosed substantially purified Helicobacter pylori antigens of about (See columns 13-16) of 53, 51, 49 , 48 , 36, 34, 31 and 29 kDa used in the formulation of pharmaceutical compositions that contain injectable liquid solutions or suspensions, (see col. 18, lines 47-67 and col. 19, lines 1-42), buffers, adjuvants saline, dextrose, glycerol, ethanol and combinations thereof. Calenoff claims a library of Helicobacter antigens (proteins and immunogenic polypeptide epitope fragments) (see claim 13-14; col. 18, lines 48-55 and col. 19, lines 14-41). Antibodies specific for bacterial antigens are taught for the purification H.pylori proteins(see col. 19, lines 66-67 and col. 20, lines 1-56), a method of purifying Helicobacter pylori polypeptides is disclosed based upon antibody affinity purification (see Calenoff, col. 20, lines 7-11) and a method of detecting antibodies based upon antibody binding of the disclosed purified Helicobacter proteins.

c. (Instant claims 1, 19-20 and 29-30) **Ferrero et al** (1995) disclose Helicobacter urease haloenzyme (contains UreA subunit of 30 kDa and UreB: Helicobacter urease) together with a additional antigen identified to be a 54 kDa heat shock protein (see page 6499, col. 1, last

sentence bridging to col. 2, first four lines). Recombinantly produced HspB (54 kDa) was combined with cholera toxin (adjuvant in 0.1M sodium bicarbonate) as an immunizing composition (see Table 2, narrative below Table, on page 6501 and page 6500, col. 1, paragraph 3). Two methods of detecting serum antibodies to the 54 kDa Helicobacter protein are disclosed, wherein the methods were immunoblotting and enzyme linked immunosorbent assay. The biological sample was contacted with the polypeptide and the immune complex formed between the serum antibodies and the polypeptide detected (see page 6500, col. 1, paragraphs 2; Figure 2, page 6501 and col. 2, paragraph 1, page 6501). Ferrero et al anticipate the newly amended or newly submitted claims 1, 19-20 and 29-30.

d. (Instant claims 10-11, 14-15) **Bolin et al** (1995) disclose a Helicobacter pylori protein in substantially purified form of about 30 kDa (see page 383, Figure 1) and a monospecific, monoclonal antibody to the outer membrane protein (see page 383, Figure 1). (Instant Claim 14) A diagnostic method is disclosed that comprises reacting a monospecific monoclonal antibody with a biological sample to form a complex with intact bacteria in the sample. The presence of an antibody/antigen complex was detected after unbound material was removed through incubation of the sample with a detection reagent (see page 381, col. 2, Dot blot test and SDS-PAGE and immunoblotting paragraphs 5-6; Figure 2, page 383; Figure 3, page 383, col. 2, top of page). (Claim 15) The reference also discloses a method of detecting antibodies immunoreactive with a 30 kDa Helicobacter pylori antigen in a sample, wherein the sample is contacted with a 30 kDa Helicobacter polypeptide in substantially purified form and

the immune complex formed between the antibody in the sample and the polypeptide was detected (see Figure 1, page 383, col. 1 and page 381, col. 2, paragraph 5).

e. (Instant claims 1,3-5, 7,10-11 and 14-15) **Doig et al** (1994) disclose isolated Helicobacter membrane proteins of 31, 48, 50 and 51 kDa together with a *pharmaceutically acceptable carrier*, specifically milli Q water (see page 4527, col. 2, paragraph 3, last two sentences). (see page 4527, col. 1, paragraphs 3-4; page 4528, Table 1; page 4530, Figures 3-4). Inherently the 50 kDa protein would evidence the N-terminal amino acid sequence claimed (claim 4).

(Instant claims 10-11) Monospecific, monoclonal antibodies were produced and found to be immunoreactive with 31, 48, 50, 51 and 60 kDa antigens (see material and methods section and Table 1, page 4528). Antibodies were diluted in a pharmaceutically acceptable carrier: 10mM Tris-HCL, 0.9% NaCl-0.05% Tween-20, pH 7.5 (see page 4528, col. 1, lines 1-2 and page 4527, col. 1, paragraph 5 (definition of TTBS provided).

(Claim 14) The reference discloses a method of detecting Helicobacter in a biological sample, wherein the monospecific antibody is contacted with a biological sample to form an immune complex with the Helicobacter pylori polypeptide to which is it specific. The complex is then detected (see page 4528, col. 1, paragraph 2 and page 4529, Figures 1 & 2).

(Claim 15) The reference discloses a method of detecting an anti-Helicobacter pylori antibody in a sample, wherein substantially purified antigens are separated by gel electrophoresis and electroblotting then immunoreacted with a biological sample to detect the presence or absence of antibody contained therein. (see page 4527, col. 1, paragraph 3-4; Table 1 on page 4528; col. 2, paragraphs 2-4 and page 4529, col. 2, paragraphs 1-4; and page 4530, Figures 3 and 4).

f. (Instant claims 1,5-6, 10-11 and 15) **Alemohammad** (US Pat.5,262,156) does disclose Helicobacter pylori proteins of about 31 kDa, 33 kDa, 54 kDa in a pharmaceutically

acceptable solution of phosphate buffered saline (see col. 6, lines 63-65; col. 7, line 40) .(Claims 10-11) Affinity purified antibodies to using Helicobacter antigens were produced (column 7, lines 40-55). These antibodies in turn were used as a control for a diagnostic method. The purified antigens were formulated into a diagnostic method for the detection of antibodies to the Helicobacter in a sample.

g. (Instant claim 1, 3-6,7, 15,19, 20, 22-24, 28-29) **Pronovost et al** (US Pat. 5,814,455 and 5,846,751) disclose Helicobacter pylori antigens of 29 kDa, 31 kDa, 45 kDa, 52 kDa, 56 kDa in substantially purified form (see all claims) together with phosphate buffered saline, a known pharmaceutically acceptable carrier (see col 5, lines 4-5). A method of detecting antibodies in a biological sample, through detected the presence of polypeptide/ antibody complexes (see Example 4, col. 11-12) is disclosed.

h. (Instant claims 7, 10, 11, 14, 18, 19, 20,23-24) **Ruiz et al** (WO94/06474) disclose Helicobacter urease or immunogenic fragments thereof (see Figure 4a and 4b, UreA is about 30-35 kDa on an SDS PAGE gel and UreB is another Helicobacter antigen; page 2, lines 33-37 and page 3, lines 9-12; page 10, Table 1) together with a pharmaceutically acceptable carrier. The urease antigen is disclosed to be in association with an additional Helicobacter antigen (proteins associated with fragments of the enzyme (see sentence bridging pages 4-5). A method of detecting Helicobacter protein antigen in a biological sample is disclosed monospecific antibodies are immobilized on a solid phase and reacted with a biological sample to form a complex (see page 8, lines 8-37 and page 9, lines 1-6).

New Claims/New Claim Limitations/New Claim Amendments/New Grounds of Rejection

Claim Rejections - 35 USC § 101

28. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

29. Claim 17 is directed to immunogenic fragments of any protein of claim 1, the fragments are not isolated and purified and read on a product of nature; the claimed invention is directed to non-statutory subject matter.

Claim Rejections - 35 USC § 112

30. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

31. Claim 16, 19, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is directed to a process for purification of a protein, and sets forth the process in the passive voice "is". The process is not distinctly claimed; this rejection could be obviated by amending the claim to recite active voice process steps, such as --subjecting--. The sample of

claim 16 is subjected to affinity chromatography but the protein is not obtained or isolated, merely subjected to affinity chromatography. How is the protein considered to be purified if it associated with an affinity chromatography column?

Claim 19 recites the phrase "further consisting essentially of an additional Helicobacter antigen". While the addition of additional components to the composition of claim 1, from which claim 19 depends is clearly permitted as long as the novel and unobvious characteristics of the claimed composition are not changed, it is not clear what the now claimed genus of Helicobacter antigens are that have this ability are as these antigens have not been defined in the instant specification. Absent a specific definition, and the knowledge in the art provided in the publication to Tomb et al (1997), Helicobacter pylori has over 15,000 open reading frames that could encode various proteins, and there are over 20 known species and strains of Helicobacter in the art at this time. What is the additional antigen that can be added, so the composition will "consist essentially of " an additional antigen? The claim is being read to recite open language "comprising" in the absence of a definition of what is encompassed by the phrase "consisting essentially of".

Claims 29 and 30 recite the phrase "appears to be of the order of 54 kDa after electrophoresis on a 10% polyacrylamide gel in the presence of SDS and an" "(claim 29) additional Helicobacter antigen" or "(claim 30) adjuvant", respectively. Does the relative molecular weight of the claimed protein appear to be 54 kDa only when in the presence of SDS and the additional component? The claim appears to require the presence of an additional

component for the apparent molecular weight to be of the order of 54 kDa; is this what is intended by the claim language?

Conclusion

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
August 21, 2002

NITA MINNIFIELD
PRIMARY EXAMINER
8/22/02